SOME COMMENTS AND DISCUSSION

ON THE PAPER

"THE ETIOLOGY OF TUMORS."

Read before the Pathological Society of Philadelphia, April 28, 1881,

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ON DR. H. F. FORMAD'S PAPER

"THE ETIOLOGY OF TUMORS."*

PATHOLOGICAL SOCIETY OF PHILADELPHIA, OCTOBER 27, 1881. The President, Dr. S. W. GROSS, in the Chair.

COMMENTS BY THE AUTHOR.

IN the paper which is the subject of discussion this evening I endeavored to prove the proposition, viz., that all *primary* tumors, save the purely congenital neoplasms, are direct products of the inflammatory process.

A certain class of tumors are admitted by several pathologists to be due to inflammation; I ascribe this cause to nearly all tumors. Again, those pathologists regard inflammation only as an exciting cause, provided there is a predisposition to tumor-formation. I am inclined to regard the inflammatory process as the factor which creates this predisposition, and hence consider inflammation as a direct predisposing cause for all true tumors. This is the difference between the view held by the real authorities of the inflammatory theory—S. D. Gross, Virchow, and Samuel—and the view which I advocate.

The idea of an inflammatory origin of tumors begins of late to gain more and more ground among the working pathologists. Several of the true tumors are nearly generally admitted to be due to inflammatory causes, and, although no one expresses himself decidedly upon the subject, I do believe that all will ultimately return to the view which the fathers of pathology originally held.

My studies on the etiology of tumors are by far not completed: still, I bring the work forward in its present state in order to get the full benefit of criticism. I want advice and co-operation; I desire to learn whether the new facts which I obtained by microscopic and other studies may admit of an interpretation different from that which I gave them. At any rate, I consider my work only an attempt at the solution of the question of the etiology of tumors, a question so much neglected and which imperatively demands active work and not hypotheses.

Before I enter into a review of my arguments I desire here to call attention and to define more closely the purely congenital anomalies called "tumors," for which I am unable to prove an inflammatory cause.

The question first arises, what is a tumor and what is not a tumor?

In the sense of Virchow, any circumscribed elevation over a given surface, or any excessive enlargement, is considered a tumor. The products of specific inflammation, such as tubercle, gumma, glanders, lupus, and lepra, also the cysts and most of the monstrosities and the hypertrophies, would consequently belong here.

I consider the following neoplasms which are composed of new-formed or overgrown tissues as *true* tumors:

Fibroma.
Lipoma.
Chondroma.
Osteoma.
Leio-myoma.
Myxoma.
Lymphoma.
Sarcoma.
Glioma.
Papilloma.
Simple epithelioma (as represented by corns, horns, onychoma, etc.).
Carcinoma.
Tyroma (tubercular tumor).
Gumma.
Lupus, lepra, and glanders.

The following congenital neoplasms I consider as simple anomalies or *false* tumors:

Angeioma.

* The paper has been published in full in pamphlet form by order of the Society. An abstract of it, entitled "The Inflammatory Origin of Tumors," appeared first in Seguin's "Archives of Medicine," October, 1881.

Lymphangeioma.
Some keloids and other nævi.
Rhabdo-myoma.
Adenoma.
Dermoids and
Other cysts.

All these last-named neoplasms should be excluded from the tumors. I suggest this, not because I cannot prove their cause directly to inflammation, but because they are simple anomalies or malformations, just like a supernumerary finger. Nobody can acquire any of them except the ordinary cyst. The individual must be born with them. Cohnheim calls them properly "monstrosities."

It is, however, possible that even here inflammation is concerned to some extent. Smallpox and syphilis, which are inflammations, are known to affect the fœtus in utero. Why, then, could we not have tumors as pre-natal inflammatory products? Still, I do not want to base my arguments on hypotheses. The fact is that children are born with large or small masses of any one of the above-mentioned congenital neoplasms.

Objection might be raised to the inclusion of adenoma in this category; but I have here reference mainly to the heterotopic adenoma, the perfect homologue of the mammæ, which grows prominent only at puberty, simultaneous with them, and governed in time and growth by the same laws. The glandular acini which gave rise to the adenoma and those from which the mammary glands started were both deposited in the fœtus, and in both were dormant up to puberty, when they developed to structures perfectly alike, the difference being only that the one has its physiological purpose and location, and the other not. The histological distinction between them as given by authors I was not able to see, after having examined *every* part of the structure. The homotopic adenomata, as occurring in connection with glands, are simple hypertrophies of any one of the racemose glands, or of a part of one.

The dermoid cysts are the best representatives of this group of anomalies. It is well established that they are simple local invaginations and misplacements of mainly epiblastic formations during early fœtal life. Certain parts of organs, such as skin, hairs, glands, teeth, etc., which usually are represented in these anomalies, proceed to full development and size and no further. There is nothing pathological in these structures except the location, unless combined with other new formation.

Ordinary cystic formations are also frequently met with in the fœtus, although many cysts are acquired in later life by the agency of various pathological factors, including inflammation. Frequently tumors are the seat of cystic formation due to degeneration or softening in their interior. The formation of cysts is nearly always a passive process. Many arise from mechanical obstruction of outlets of glands, or from exudation of liquid into closed cavities. None of them has anything in common with tumors except the tumefaction.

Angeioma and lymphangeioma and the keloids are exclusively congenital formations; they even seldom present themselves as tumefactions, and only then if subject to cavernous change and combination with other lesions. There is no reason why these anomalies should be classed with the tumors.

The same may be said concerning rhabdo-myoma, the strictly congenital rare new growth, made up of misplaced striated muscular tissue.

It is in these congenital neoplasms alone that an inflammatory origin is not clearly evident.

OTHER VIEWS.

Without entering into details, I will at this point enumerate the other theories on the etiology of tumors.*

Those theories, although held by high authorities, and ingenious as they are, hardly go beyond the level of pure hypothesis. Hypotheses and speculations are easily disposed of by facts like those presented in favor of an inflammatory origin of tumors.

No tumor has ever been *proven* to have originated *spontaneously*, or to be produced by a certain *dyscrasia* of the blood, or by *nervous influences*. We are not more justified in applying this or that pet hypothesis for the etiology of tumors without proving it, than to declare a house to have arisen through the instrumentality of mysterious forces because we do not know who built it, and do not care to inquire by whom and how it was built.

The evolution and involution of tissues

* In my monograph, "The Etiology of Tumors," I gave all these views in full.

as conditioned by age, referred to by Thiersch and Rindfleisch, and best explained by Dr. Ch. B. Nancrede (in his highly suggestive communication to the Pathological Society, 1876), are regarded as important predisposing factors in tumor-formation, which at the same time decide the variety of tumors.

There can be no doubt that evolution and involution of the tissues influence the kind of tumor-formation; but I do not believe that these conditions in themselves predispose particularly to tumors, even in the presence of an over-supply of blood. We want certain changes in the integrity of the tissue (to be referred to later), and these can be brought about by the inflammatory process alone,—by nothing else.

Due credit must also be given to Cohnheim for his embryonal theory of tumor-formation. Cohnheim uses the well-established congenital derivation of the dermoids, rhabdo-myoma, angeioma, etc., as a basis for his hypothesis, and jumps at once to the conclusion that all tumors are congenital and of embryonal origin. Some new formations which he admits to be of inflammatory origin—viz., gumma, tubercle, lupus, neuroma, osteophytes, etc.—he excludes from the category of true tumors.

But how great a reduction in number will Prof. Cohnheim's list of true tumors experience should it be proven that all tumors are of inflammatory origin save those few congenital formations which I suggest to exclude from the list of true tumors!

Epstein (*Zeitschr. f. Heilkunde*, i., 1880) believes to have found anatomical proof for Cohnheim's hypothesis. He observed epithelial pearls in the mucous membrane of the gums, tongue, and genitals of newborn infants, and regards them as the famous supernumerary embryonic collection of cells. This, I think, is a great error. It has been shown by several observers that wherever squamous stratified epithelium exists epithelial pearls may be found,—viz., in the epidermis and in all epiblastic mucous membranes. I believe that the arrangement of epithelium into pearls is always a sign of retrograde change, and, as well as the arrangement of any kind of cells into nodes, signifies usually an ante-mortem act of cells, and not "dormant supernumerary embryonal collections."

To find further proofs for the embryonal theory of Cohnheim, his pupils made extensive experiments. They succeeded; and the successful results, which were supposed to give a firm basis to the embryonal theory, were announced to the world in the renowned *Archives of Virchow*.

Unfortunately, however, the trifling efforts of American workers in experimental pathology gave results entirely opposed to those obtained by Cohnheim's pupils, and have probably forever demolished the beautiful embryonal theory of the etiology of tumors, as will be shown farther on.

EXPERIMENTS.

Allow me now to reflect one moment upon the results of the experiments made with the object of ascertaining the cause of tumors. I will review here only the main points of interest; the details are given in my monograph.

So far only little success was obtained in this line by experiments. Still, this much can be ascertained from them:

First, that tumors cannot be inoculated by virtue of any infective or specific properties; and

Second, that small living particles of tumors can be successfully transplanted from man to animals, and upon transplantation may continue to grow.

No one of the experimenters really succeeded to "inoculate" a tumor with tumor-juices except in a few very doubtful instances.

The juices as occurring in malignant tumors are always the products of degeneration of the tissue or cells composing them. The cells suspended in that juice are dead, having undergone fatty or some other degeneration, and this is the reason that injection with juices fails. If particles of living tumor-tissue happen to be suspended in that juice, "inoculation" might succeed, but not with mere pure tumor-juice. In the few apparently successful inoculations with juices, particles of perfect tumor-tissue undoubtedly were injected together with them.

The notion of a specific tumor-virus held by some of the highest authorities is thus fully disposed of.

There are recorded a number of successful transplantations of tumors: *i.e.*, small fragments of tumors when put into the subcutaneous tissue of animals grew and enlarged in size as long as observed, if conditions were favorable.

This, however, does not prove anything for the etiology of primary tumors. It has been shown that if a cock's spur be transplanted from the leg to the comb it will often grow excessively; another most perfect parallel to transplantations of tumors we have in skin-grafting and in plastic surgery.

Other observers, again, impressed with Cohnheim's idea that tumors arise only from misplaced (heterotopic) cells or tissues, experimented as follows:

1st. Particles of tissues taken from *adult* animals were introduced into the circulation and into the interior of organs, but they failed to grow and were ultimately absorbed.

2d. Fœtal tissues (particles of embryonal cartilage, etc.) were similarly transplanted, and they grew and developed to moderate-sized tissue-masses (tumors).

Through these results Cohnheim's proposition that tumors arise only from misplaced *embryonal* cells was regarded as proven.

But this was too hasty a conclusion, and it appears also that those experiments were conducted very carelessly, as the results could not be confirmed.

The exhaustive experiments which Henry Wile made in the pathological laboratory of the University of Pennsylvania (partly quoted in my monograph and partly not published yet) positively prove that transplanted *adult* tissues grow as well as fœtal ones, and never became absorbed in carefully-executed experiments. The results of these experiments surely indicate conclusions far different from those which were derived from the experiments performed in the Leipsic laboratory. As the embryonal theory of Cohnheim depended upon the results of the latter experiments for its main support, it no longer can be regarded as proven, and all the much-dwelt-upon deductions therefrom are wholly unwarrantable.

INFLAMMATION AS THE SUPREME CAUSE.

Allow me now to review the arguments in favor of, and the proofs for, an inflammatory origin of tumors, as brought forward in my paper. These are of three kinds: 1st, proofs by analogy; 2d, clinical and statistical proofs; and 3d, microscopical proofs.

1. *The close analogy of tumors and inflammatory products is strongly in favor of our proposition.*

Careful study and comparison have shown that no line of distinction can be drawn between true tumors and chronic inflammatory products; in fact, many of the latter are recognized as true tumors.

The criterion of true tumors is regarded to be their tendency to permanency in contradistinction to inflammatory products, which tend to disappear. The cases collected and the views of reliable observers recorded in my monograph show this to be incorrect. It has been proven that tumors occasionally heal and disappear. On the other hand, it is well known that only acute inflammatory products tend to disappear, while many chronic ones never do disappear, and that the symptoms and cause of the latter are frequently less obvious than in the case of tumors.

The connective tissue which, in proliferating, constitutes the main bulk of elephantiasis and of the cirrhosis of organs and a good many other pathological tissues outside of tumors, never disappears.

Virchow properly considers elephantiasis Arabum and soft fibroma morphologically and etiologically identical, and in the same sense he does not admit any difference between the connective tissue of an advanced cirrhosis of organs and that of a diffused fibroma. In fact, we are only in the habit of calling a proliferation of connective tissue in the mamma an intercanalicular fibroma, because the connective tissue affects an external part, while a similar affection of the liver or kidney we term an inflammatory one—a cirrhosis. Why should we make such a distinction?

Gummata, tubercles (tyromata), lupus, the well-established products of inflammation, are unquestionably true tumors.

Lucke observed that sarcomata in young individuals occasionally grow as rapidly as acute abscesses, and have been frequently mistaken for the latter.

Tissues which are most liable to be the seat of inflammation are also the most *common seat* of tumors. Again, those tissues which do not participate in active inflammatory processes (ganglionic and striated muscular tissue) seldom or never give rise to tumors.

The extensive and careful statistics of Dr. D'Espine, of Geneva, show that the os uteri and the stomach are the most frequent seats of primary cancer, and they are also distinguished for their remarkable liability to catarrhs. Virchow has repeatedly

pointed out in a catarrhally inflamed gastric mucous membrane the gradual transition to carcinoma, a fact observed also by Dr. J. H. Musser and myself.

The healing process in malignant tumors (wherever it occurs) is precisely the same as that of an ordinary granulating ulcer. Here and there, healing is accomplished by the additional formation of connective tissue,—*i.e.*, cicatrization.

But the most beautiful analogy between tumors and inflammatory products is demonstrable by the microscope, which led to the discovery of new and important facts.

2. *Clinical and statistical proofs.*

My own experience is limited, but in the cases of tumors in which I had the opportunity to get the history myself, or where I insisted upon an exhaustive anamnesis in cases of others, it was possible in nearly one-half of the cases to trace out a local inflammatory process preceding the tumors at some time or other. Sometimes it dated years back. Careful inquiries nearly always revealed some cause,—viz., an injury, long-standing irritation, mechanical or toxic, or an impaired or excessive use of the part, pressure, or a long-standing catarrh, or something of that nature.

It is also an established fact that those organs and regions of the body which, from their position and their function, are most exposed to injuries or irritation are the most usual seat of tumors. This is proven for the orifices of the digestive and genito-urinary tract, which are so much exposed to injuries and are also classical seats of especially malignant tumors.

Primary cancer of gall-bladder has been repeatedly traced to gall-stones; that of the urinary bladder to a similar cause.

For surface-cancers an inflammatory origin may safely be regarded as proven. I know of scores of epitheliomata which had been traced to little sores produced by injury. Nearly all those everlasting leg ulcers are epitheliomata.

It is just here that the influence of evolution and involution of tissue upon the variety of tumor does not hold good. Repeatedly have I seen epitheliomata of lower extremities in young persons directly produced by injuries, burns, etc. (Clinical service of Prof. Agnew.)

Who will deny the inflammatory origin of the very common epithelioma of lip? or that of tongue or penis?—the first nearly exclusively occurring in smokers, the second always being associated with injury of tongue by sharp teeth or otherwise, and the third with congenital or acquired phimosis.

Chronic inflammations of the skin, as occurring on workers in coal-tar and paraffin manufactories, etc., commonly lead to epithelioma. A similar origin has the chimney-sweeper's cancer.

It has been proven that long-continued catarrhs of stomach (particularly in drunkards) lead to cancer.

Through irritation and injury common warts and scars are produced; further repeated injuries very frequently convert them into malignant tumors (cancers, sarcomata).

Prof. Agnew removed from the back of a middle-aged person a sarcoma developed secondarily in a scar. Some time previously he had removed (from the same patient) from the same spot, or from above that spot, a lipoma.

Sarcomata are commonly due to direct injury; neuromata exclusively so.

Glioma and tyroma, as met with in the brain, are nearly always traceable to falls and blows.

Hundreds of cases of fibroma, lipoma, chondroma, and osteoma have been traced by distinct and clear histories to pressure and irritation, or directly to blows, fractures, cuts, and other injuries.

Winkel, who investigated exhaustively the etiology of fibromata and myomata of the uterus, came to the conclusion that these tumors are caused either by direct excitants, viz., coition, injury, abortion, rough removal of placenta, cellulitis, or, indirectly, through repeated lifting, shock, sudden hyperæmia, etc.

No reliable line ofdistinction can be drawn between the lymphomata and lymphadenitis.

Any one can convince himself of the above-mentioned facts by just looking carefully over the literature, and by taking careful histories of his own cases. Hundreds of tumor cases of positively traumatic origin are also recorded in the classical works on tumors of Virchow, Weber, Müller, and Broca.

Unfortunately, however, these facts are not generally known; the literature is not sufficiently studied, and the histories of tumor cases are not sufficiently carefully inquired into.

Inflammation is the only factor which

has been traced to be the positive cause of tumors in a number of cases. This is proven by high authority and statistics. But as these authenticated cases of inflammatory origin are in moderate number, and as those with no cause (by reason of careless note-taking) are in enormous majority, the inference is drawn that inflammation has little or no significance in the pathogenesis of tumors.

I beg leave to argue as follows. In a certain number of cases it is positively known that inflammation preceded and was the cause of the new growth. In regard to the remaining cases of tumors we know nothing; no positive cause could be traced. Hence I think it logical, for the present, to consider inflammation as the cause of all true tumors. All other alleged causes are only speculations, and nothing reasonable can be brought forward against the inflammatory theory. Speculations are valueless, I think, in the presence of positive facts, even if these be few in number. In science any amount of negative results are always disregarded in the presence of even a few positive facts. *Until contrary proof be given, we are at present, by a mass of evidence, forced to the conclusion that tumors represent merely one of the terminations of inflammation.*

3. *Microscopic proofs.*—Here I will make the following abstract from my first paper:

The question now arises, in what way does inflammation produce a tumor, and why and when does a tumor develop after an injury? Why is not every injury followed by a tumor, if inflammation is the cause? Prof. Maas's* ingenious answer was that it depends upon the presence or absence of Cohnheim's supernumerary embryonic cells at the seat of the injury. If those misplaced or aberrant cells happen to be present in a part, a trauma will induce inflammation, followed by a tumor; if no extra cells are present, a simple inflammation will follow, and nothing more. But this is only a hypothesis; it cannot be demonstrated. Embryonal (fœtal) cells could not continue to exist unchanged in the adult individual; nor do they need to be pre-existing in order to form a tumor. They can be and are always created by any inflammatory process.

I will try to answer the above question by facts which microscopic examination reveals, and which will show that the study of histogenesis must go hand in hand with that of the etiology and possibly might disclose the mysteries of the cause of tumor.

It is true that not always direct observation of active pathological processes can be made. In the case of tumors, only inferences of previous cell-activity can be drawn from the microscopic picture; but the pathological process can frequently be traced out under the microscope, from the various transitional stages of the elements of the new forming or formed tissue.

It is in accordance with the modern views to say that every tumor has its strict physiological prototype. Even for the cancer, only the peculiar atypical arrangement of the cells remained a criterion, while the cells themselves are supposed to be strictly identical with those found normally.

It appears to me, and the more I study the histology of tumors the more I become convinced, that any variety of cells composing a tumor are not identical with those found normally, but resemble those met with in chronic inflammatory products.

In tumors, the shape and the peculiar variations in size of the cells and nuclei, the character of the intracellular net-work and of the amœboid motion of certain cells, the intercellular substance, the occasional arrangement into nodes, the relation to reticulum and blood-vessels, and the peculiarity of the latter, are all precisely like what is found in chronic inflammatory products and not like in normal tissues.

There is a great difference between the tissue-elements of fibroma and those of normal connective tissue, for example.

I shall give briefly the details of my investigation of the structure of fibroma, which, when completed, will be published and illustrated elsewhere.

Concerning the structure of normal connective tissue, the following seems to be generally established and in good preparations quite demonstrable:

The ultimate connective-tissue fibrils (the fibrillar variety) are in varying number united together to form bundles; these again occasionally unite to form larger bundles; these bundles arrange themselves at different localities in various manner, *i.e.*, parallel as in tendons, or as a lattice-work in membranes, or decussate at different angles and in all possible directions in all other localities, leaving between small spaces, these spaces being dependent for their shape and size upon the arrangement of

* Berliner Klin. Wochenschrift, No. 47, 1880.

the bundles. They communicate with one another, and thus form a system of channels throughout the whole connective-tissue system of the body. These channels contain a small amount of fluid containing *mucin*, and they are the receptaculi of the sometimes enormous quantities of serum in œdema. These same spaces or channels may also get filled with air, producing emphysema in skin and other parts of the body.*

Von Recklinghausen has shown that the spaces in the connective tissue communicate with the lymphatics, and he calls the spaces juice-channels; they act as "vasa serosa" (Orth), conducting the serum from blood-vessels to the lymphatics, and "feeding" (Tyson) the tissues.

By the nitrate of silver method of Von Recklinghausen, which is now the common property of all the laboratories of the world, it can be easily demonstrated that each of the connective-tissue bundles spoken of is surrounded by a distinct membrane composed of large flat cells. These flat, so-called endothelial cells are very thin, nucleated, and are closely united at their periphery with one another, so as to form continuous membranes or sheaths, which envelop each or several fibrillar bundles and thus at the same time form a lining for the spaces between them. Without nitrate of silver the endothelial cells cannot be seen; all that is seen are the nuclei of the cells, round or oval in shape if viewed from above, or spindle-shaped if the whole cell is seen in profile. I will not enter into further details here; this suffices to make myself now intelligible concerning some points in the histology of connective-tissue tumors, particularly fibroma.

I investigated by the nitrate of silver method three specimens of fibroma: 1st, a small, hard fibroma from the finger of a girl, æt. 20, developed from the tendon; 2d, one of the size of two fists from the broad ligament of a woman, æt. 35; and 3d, an intra-uterine fibroma of the size of one fist, from a woman, æt. 40.

I might say at the outset that in the preparation of the first and third specimens I failed altogether to discover any perfect endothelial sheaths surrounding the bundles of fibres, which were so beautifully seen in a preparation of tendon made for comparison simultaneously with the fibroma specimens. In specimen second only a few perfect endothelial sheaths were visible. The microscopic picture of one of the silver preparations (from specimen No. 1) was this. The fibrils were on the average much thicker than in normal connective tissue; some running straight, others rather wavy and not quite parallel with one another, frequently decussating. Only few perfect fasciculi or bundles of fibres were seen, but most of them had not a trace of endothelial ensheathment. Some had a partial endothelial sheath in some places, and here the bundles appeared constricted. In several places were seen irregular protoplasmic masses apparently in connection with the fasciculi and proved to be partially detached endothelial cells. Between the bundles were seen several groups of young indifferent cells, resembling white blood-corpuscles. Other cells were double the size of the latter, some spindle-shaped and with prominent nuclei. The latter were seen occasionally in a state of division or were already divided. They resembled remarkably the germinating endothelial cells from serous surfaces, as described by E. Klein of London, represented by him in his Atlas of Histology, Plate VI.

I interpret the microscopic picture as a whole thus. The endothelial cells composing the sheaths of bundles of connective tissue have become isolated, and hence the sheaths are destroyed. The boundaries being removed, the liberated connective-tissue elements grow with great vigor. The growth is perhaps promoted yet more by the presence of the serum of the juice-channels, with which the cellular and fibrillar elements now come in direct contact, the sheaths being destroyed. The cells and fibres here, like in elephantiasis, "feed" (as Prof. Tyson would say) upon that serum in which they are soaking. The endothelium is proliferating (germinating, *Klein*), and probably gives rise to those groups of indifferent cells which evidently form the main source of the new growth. Foerster† has pointed out that in the development of fibroma the fibres arrange themselves more or less concentrically around and develop from these

* The subcutaneous tissue of the whole body can be filled with air, so as to produce enormous emphysematous disfiguration, by forcing air through blow-tubes at a few points or possibly even from only one point of the body below the skin. I have seen children purposely prepared in this way for beggars' purposes.

† Atlas der mikroskopischen und pathologischen Anatomie, Leipzig, 1855.

islands of cells, thus giving rise to the lobulated appearance of this new growth. It is also very probable that emigrated white blood-corpuscles assist in forming those collections of cells.

What interests us at present, however, is the absence of the endothelial sheaths in the connective-tissue bundle in the fibroma, and that this feature fibroma has in common with all connective-tissue formations which owe their origin to inflammation, as will be shown directly.

I can affirm the absence of endothelial sheaths in the new-formed fibrillar connective-tissue as met with in cirrhosis of organs which invariably accompanies the proliferation of the alveolar connective tissue in such situations. It would be very desirable that other histologists would undertake research in this direction.

Cornil and Ranvier* describe the disappearance of the endothelial ensheathments in connective tissue which is the seat of inflammation. They describe the appearances as follows: "The fasciculi are smaller; less distinctly fibrillar; they do not appear to be enveloped by a special layer which limits them and which causes them to swell irregularly when acted upon by acetic acid." Cornil and Ranvier consider that the "large flat cells" are replaced by embryonic tissue.

The inflammatory process is, to my knowledge, the only factor which can disconnect or isolate endothelial or epithelial cells united together to form a certain lining or covering. Let us take, as an instance, the lung. The flat cells which form the lining of the air-vesicles are so closely united or grown together in the normal adult individual that no means at our command at present can isolate them. But in catarrhal pneumonia the inflammatory process demolishes that lining instantly, the cells which compose it "return to their embryonic state" (Stricker), they become completely isolated.

The abnormal increase in bulk of tissue in both the fibroma and the inflammatory connective-tissue products, appear to me to be due to the same cause:

1. The removal of the boundaries which keep the fibres intact, viz., the destruction of the endothelial ensheathments.

2. The proliferation of the endothelial cells of these destroyed sheaths and of the connective-tissue elements themselves, and probably with the aid of white blood-corpuscles.

If the endothelial sheaths of the connective-tissue bundles and other normal boundaries are re-established in the inflamed tissue, then it will return to its normal state, or in case of loss of substance will heal by permanent scar-tissue. The healing process was perfect.

On the other hand, the same tissue will give rise to a fibroma if this healing process was imperfect; *i.e.*, the endothelial ensheathments are not re-established, the connective-tissue elements remaining freed from any restriction proliferate on their own accord, grow above the physiological limit, and thus inflammation terminates in a tumor.

Hence, from histogenetic grounds, I would suggest that *fibromata should be classed as a product or rather as one of the terminations of inflammation.*

This is also in accord with clinical experience.

Now, is an inflammatory origin less evident in other tumors? Can there be shown any positive microscopic difference, for instance, between a mass of inflammatory granulation tissue and a sarcoma? It cannot. To my knowledge, distinguished histologists have repeatedly had sad experience in this.

If the discoveries of Classen and Woodward should prove correct, we would, to my mind, have another additional proof that cancer is only one of the terminations of inflammations. I will quote the following:

Woodward† says, "My own studies of thin sections lead me to the conclusion that the migration of white blood-corpuscles played a great rôle in the development of cancerous growths, and that at least in certain cases the cancer cylinders were formed by the transformation of these corpuscles, which first accumulated in the lymphatic capillaries and the passages leading to them."

Classen‡ is even still more positive, saying that he has proven "that the cells of cancer cylinders and all the elements of cancerous growths are no other than migrated white blood-corpuscles escaped from the blood-vessels."

* A Manual of Pathological Histology, translated by Shakespeare and Simes, Philadelphia, 1880.

† The Structure of Cancerous Tumors. Toner Lectures, Washington, 1873.

‡ Ueber Cancroid der Cornea etc., Virchow's Archiv, vol. l., 1870.

Though in my own research I did not succeed as yet to confirm the observations of Woodward and Classen, they are possibly correct, and I utilize them as coming from such high authority. Besides, they correspond so remarkably to what I believe to have established for fibroma.

My view of the histogenesis of fibroma holds good also for primary glandular carcinoma.

The glandilemma or basement membrane in glands (wherever such exists), upon which the epithelial cells rest, may be destroyed in precisely the same manner as the endothelial sheaths of the fibrillar bundles. This is demonstrable in carcinoma beginning to develop in a gland, or in the transformation of an adenoma into cancer. Here, as in fibroma, only an inflammatory process can accomplish this destruction of the normal boundaries. These boundaries, if not re-established after an injury by perfect healing, there is nothing to prevent the epithelial cells from travelling into surrounding connective-tissue spaces and to thus form a cancer.

I have here reference to the destruction of the endothelial boundaries which forms the basement membrane of the epithelium alone. The endothelial ensheathment of the connective-tissue alveoli remains perfect in the cancers unless it becomes inflamed.

It is not the want of resistance of the surrounding tissue (as is generally held), but simply the getting loose of the normal cells from their place of attachment, which constitutes the formation of a malignant tumor.

It is the mobility of the cells, I think, that conditions the malignancy of a tumor. Any tumor, even the most benign one, would be eminently malignant if the cells composing it could get loose and travel through the widely open paths of the system of juice-channels.

In benign tumors the cells are more or less fixed, hence no metastasis. The endothelial basement membranes and ensheathments are, however, here also defective. The physiological boundaries which maintain the equilibrium and keep the cells in position and in harmony with one another are found absent in that tissue which gave rise to tumor-formation.

As it is not proven so far that any other pathological process besides inflammation is capable of destroying the endothelial ensheathments and basement membranes, I am driven to the conclusion that all true tumors are direct products of the inflammatory process, and that true tumors should be considered as one of the terminations of inflammation.

DISCUSSION.

Dr. S. W. Gross said that the main propositions propounded by Dr. Formad were, first, that all tumors are the products of the inflammatory process, and, secondly, that in the development of tumors there is a destruction of normal boundaries. Gumma and tubercle are regarded by the author as tumors; but Dr. Gross thought that the term should not be applied to the temporary products of specific inflammations, but that it should be restricted to permanent additions to the normal tissues. Dermoid cysts ought certainly to be included, as should also angeioma and lymphangeioma. The former naturally comes under the classification of cystic growths, while the latter—in regard to the causation of which Dr. Formad confesses that he has strained a point—are not merely congenital enlargements of pre-existing vessels, but are composed partly of newly-formed vessels, and should, therefore, be retained among the neoplasms. While it is true that in carcinoma of the breast the membrana limitans, or glandilemma, of the acini and ducts is destroyed, it is equally true that it remains intact in adenoma of that organ: so that, in the formation of tumors, normal boundaries are by no means always destroyed. Dr. Gross was convinced that inflammation, or a process nearly related to it, plays an important part in the etiology of many tumors, but he thought that Dr. Formad was too exclusive in his theory. He, moreover, believed that Dr. Formad was too sweeping in his assertion that inoculation with the juice of neoplasms was incapable of begetting similar growths. Dr. Formad, indeed, quotes several experiments which disprove his own positive assertions; and Dr. Gross related the following cases, which he thought supported the doctrine of the inoculability of tumor-juices.

The first case shows that sarcoma may be transmitted to man from an animal, and the second and third demonstrate infection in the same individual other than by metastasis.

Case I.—An ox was affected with a subcutaneous tumor behind the scapula, which proved, on removal, to be a medullary sarcoma. A few days before the operation the owner made an incision into the swelling on account of pseudo-fluctuation, and there was a sanious discharge for some days. The wife, æt. 23 years, was in the habit of cleansing the part, and had at the time a small wound on the outer side of the fourth finger of the right hand. In a few days a small warty excrescence was noticed on the finger, which soon

became the seat of burning pain, and attained a diameter of fifteen millimetres in a month. It was covered by a whitish-gray pellicle, and Dr. Kuhn, of Niederbronn, found it to be a medullary sarcoma. (*Magazin für die Gesammte Thierheilkunde*, 1862, p. 328.)

Cases II. and III.—Dr. Reinecke, of Hamburg, has recorded two examples of the inoculation of the canal formed in tapping the abdomen in carcinomatous peritonitis. In both the primary disease was cancer of the ovary, with secondary affection of the mesenteric glands and the peritoneum, resulting in ascites, for which paracentesis was performed, five times in the first case and twice in the second. In both instances cancerous nodules appeared in the track left by the trocar, which, on post-mortem inspection, were not found to be continuous with the carcinomatous peritoneum, but separated from it by a layer of sound tissue. (*Virchow's Archiv*, Bd. l.)

Dr. TYSON thought that whatever else might be disputable as to Dr. Formad's view of the etiology of tumors, he was correct in saying that there were more facts in support of the inflammatory view than could be adduced by the advocates of other theories. This much he was willing to concede, but still thought the proposition not proven. The dyscrasia theory has been practically disproved by Virchow. The spontaneous theory has some points in its favor, and it cannot be *disproved*, although, on the other hand, it has fewer facts in its favor than has the inflammatory view. Cohnheim's theory has nothing in its favor beyond the occurrence of rhabdo-myomata, dermoid cysts, angeiomata, and lymphangeiomata, etc., which are allied congenital growths. The inflammatory view has two sets of facts in its support,—viz., the occasional operation of causes which are identical with those which produce inflammation, and the histological resemblance presented by certain tumors, as fibromata, to the products of inflammation as seen in cicatrices, and, if Dr. Formad's last observation is correct, the further histological similarity as to the absence of the limitary endothelial membrane surrounding the connective-tissue bundles. Dr. Tyson agreed with Woodward and others in thinking that the time had not yet come for a satisfactory determination of the etiology of tumors. Certain facts adduced by Dr. Formad have not the weight that he supposes,—viz., the want of permanence of tumors and the persistence of inflammatory products. The instances of both related are but exceptions to the rule. On the other hand, however close may be the resemblance of the histological elements of some tumors to those of inflammation, there are many others in which no such resemblance exists; such is the fact with regard to the carcinomata and many histoid tumors, as the chondroma and osteoma particularly. The attempt, however partially successful, is nowhere paralleled in inflammatory processes.

As to the position to be accorded to such formations as angeioma, lymphangeioma, and dermoid cysts, Dr. Tyson fully agreed with Dr. Formad that, accurately speaking, they have no place among tumors. We continue to place them there rather from force of habit than for any scientific reason. Only in one particular—their correspondence with the etymological definition of "tumor," which means literally a "swelling"—do they comport with the correct notion of tumor.

Dr. F. P. HENRY said that he could not accept the theory of the inflammatory origin of tumors except in the general sense that they, as well as inflammatory products, are the result of perversions of nutrition. Its acceptance would necessitate a change in our views regarding the inflammatory process, compelling us to speak of a fibromatous, a lipomatous, an enchondromatous, and other hitherto unheard-of forms of inflammation.

While facts such as those mentioned by Dr. Formad furnished strong evidence in favor of the inflammatory origin of tumors, it should not be overlooked that there are at least equally strong facts opposed to this theory. Chief among these were the extraordinary frequency of inflammation and the comparatively extreme rarity of tumors. If a direct causal connection existed between inflammation and tumors, the latter would be more frequent. Dr. Formad had quoted the statement of a United States military surgeon that certain tribes of Indians enjoy an almost complete immunity from tumors, and there is no doubt whatever that the mode of life of these same Indians must render them peculiarly subject to inflammatory affections.

Prof. TYSON had referred, by way of illustrating a point in favor of the inflammatory theory, to the likeness presented by fibroma to a mature cicatrix, and that presented by sarcoma to granulation tissue. These are mere coincidences. To make this illustration of value it should be proved that fibroma originates as sarcoma, which, it is scarcely necessary to say, cannot be done.

Dr. HENRY acknowledged the pleasure and profit he had derived from Dr. Formad's pamphlet, and expressed his belief that it would be regarded as a standard work of reference by those interested in the subject of the etiology of tumors.

Dr. NANCREDE said that in reading Dr. Formad's valuable paper his attention had been arrested by certain statements from which he could not but feel compelled to dissent. According to the commonly-accepted view of the process of ossification, the discovery of islets of cartilage in adult bones is precisely what one would expect, especially when we know that traces of chondrogen are found in analyses of mature portions of the skeleton. Instead of being "misplaced

germs," they are merely remains of the calcified fœtal cartilage situated at the points of mutual intersection of the periosteal ingrowths, which finally substitute all except traces of the fœtal structure. Even accepting Cornil and Ranvier's view,—which the speaker thought was, after all, reconcilable with the observations of other authors,—the "misplaced-germ" theory was utterly untenable. Dr. Nancrede thought that Dr. Formad had misunderstood his views as set forth in the quotation from his paper, as he would rank himself among the "inflammatory" as well as the "spontaneous" theorists. The speaker then gave a *résumé* of his own views, supporting them by certain positively ascertained facts as to the condition of the mammary gland at various ages, the effect of varying blood-supply to it and other organs, etc. He then stated that he considered Dr. Formad's views were incorrect as to "natural healing," or the reverse in its causative relation to morbid growths. Dr. Nancrede propounded the following: that when the irritant *and* the condition of the tissues were so related that the proliferation of cells was such as to keep pace with a sufficient blood-supply to admit of their development into tissue, normal healing occurred. If this proper relation failed to obtain, suppuration, caseation, or, perhaps, under certain circumstances, various morbid growths, would result. The speaker then mentioned certain facts which could be actually proven as to the relative atrophy of the connective tissue of the lip, the effect of continuous local irritation on the development of epithelioma, certain well-attested physiological facts, and contended that the missing links in his chain of, not reasoning, but facts, were practically demonstrable. He therefore repudiated Dr. Formad's dictum that all views but the inflammatory were mere theories,—"*that where nothing is proved there is nothing to disprove*," —and quoted from the lecturer's paper on page 46, where he contended that the conclusions were *purely* theoretical and not logically warranted. Dr. Nancrede then endeavored to show that the failure of the connective-tissue bundles in rehabilitating themselves with their endothelial investment, if confirmed, and specially if demonstrated as a weakening of the connective-tissue barrier against epithelial ingrowths, was merely due to want of equilibrium between the blood-supply of the two tissues.

Dr. CHAS. K. MILLS said that he wished to put on record, in connection with Dr. Formad's valuable paper, a few notes on ten cases of brain tumor in which the post-mortem examinations had been made by him. These were cases in which close inquiries were made as to probable causation. In the majority of them, as will be seen, a history of traumatism was given. The notes were with reference to the history and the nature of the growths, as follows.

Case I.—Fall from high door-step, striking head. Fibroma.

Case II.—Wounded in the head by glancing bullet. Gumma.

Case III.—History of blows on the head and of syphilis. Gumma.

Case IV.—History of blows on the head and of syphilis. Gumma; also softening and abscess.

Case V.—Kicked by horse on the head. Fibroma.

Case VI.—Thrown from a horse and kicked on the head. Two growths: fibroma and gumma.

Case VII.—History of syphilis. Gumma.

Case VIII.—No history. Glioma.

Case IX.— " " "

Case X.— " " Carcinoma.

Dr. E. O. SHAKESPEARE felt that he could not allow the debate to close without expressing his high appreciation of the value, to the American physician, of the labor Dr. Formad had so successfully and learnedly performed in collating from the literature of the languages of the civilized world almost all of importance that has been thought and performed by distinguished men while attempting to elucidate the cause of tumors, and in classifying and abstracting, briefly, clearly, and forcibly, the various opinions of investigators. He had listened, much interested, while the lecturer with great ability and ingenuity proceeded to unfold and support his own belief concerning the etiology of tumors, and he had given close attention to the progress of the subsequent debate. He confessed that he had made no great study of the subject in question, and therefore did not feel entitled to entertain or express any very positive opinions; yet, during the course of the reading of the paper and of the discussion which had followed it, he had become more and more convinced of the necessity of exercising great caution in the acceptance of assumptions which may have little for their justification beyond a quasi-sequential order of appearance of certain phenomena, which is often, but by no means always, recognized in the history of tumors. He very much doubted the possibility, in the present state of our knowledge, of proving that inflammation either was or was not the essential cause of tumors. Certainly the lecturer, as well as other experienced investigators, must be credited when he affirms that in the majority of cases of tumor in which an adequate history has been recorded the growth has been preceded by a local inflammation or an injury. And yet even in these cases (supposing, for the sake of argument, there were no other) what right has any one to assume that the previous inflammation has acted as any other than a simple exciting cause? and who can rationally declare the tumor to be one of the natural terminations of the inflammation?

If the lecturer thinks to have discovered a

general law concerning the etiology of tumors, let him and those who seem inclined to accept his hypothesis for one moment consider its application to syphilitic and tuberculous growths.

Dr. Mills has related, in the course of the debate, a number of cases of brain tumor, the histories of which showed that they followed a severe blow or other traumatism. In some instances the tumor proved to be sarcomatous, in others tuberculous, in others gummatous. Dr. Shakespeare referred to these particular cases because Dr. Mills had related them as perhaps offering some support to the hypothesis advanced in the paper, and had incidentally referred to him as personally cognizant of several of them. These cases are no more, perhaps no less, typical than others of that large class from which the essay has been made to deduce the general law enunciated this evening.

Will the lecturer take the position (seemingly absurd in the light of our present knowledge of syphilis and tuberculosis) that the tuberculous and the syphilitic tumors, no less than the sarcomata, are simply the natural terminations of an ordinary inflammation established by a traumatism? Or will he rather prefer to further curtail the list of tumors for the purposes of his theory, and erase the names of tubercle and gumma?

If the latter horn of the dilemma be elected, he would suggest the propriety of placing true carcinoma in a category very near to that of tubercle and gumma, for there are very many parallels and similarities in their clinical and pathological aspects.

He declared that he could see no cogent reason why some authors, in drawing the line of demarcation between abnormities which are and those which are not to be regarded as tumors, have placed upon the one side cancerous growths and upon the other side have ranged the permanent products of syphilis and tuberculosis. He did not recognize mere relative size as an adequate distinction between one morbid product which must, perforce, be a tumor, and another which must not be so classified. Carcinoma sometimes presents in its history the phase of miliary eruptions, and, on the other hand, tubercles oftentimes form a confluent tumor-mass of very considerable size and delimitation. All that is at present known of carcinomatosis and of tuberculosis would seem to warrant the belief that in both there is frequently a strong hereditary predisposition. In both, from the locus of primary manifestation of disease the system may become infected by way of the lymphatics; in both the chain of lymphatic glands along the course of the lymph-vessels which lead from the primary growth may, and often does, form a cordon to prevent, at least for a time, the contamination of the general system; in both, when the morbid influence passes these natural barriers and reaches the circulating blood, metastases in various situations usually occur.

Notwithstanding the research and the observation and the ingenuity of the lecturer, Dr. Shakespeare thought that, as yet, we have no satisfactory reasons for attributing to an ordinary traumatic inflammation any agency in the development of a tumor beyond that of a simple exciting cause.

Dr. FORMAD, in closing the discussion, said, in reference to Dr. S. W. Gross's remarks, that he did not think it probable that tumors could arise from inoculation with tumor-juices unless the latter were the carriers of living tumor-particles. He believed that even in the three cases of apparent inoculation with tumor-juices just referred to by Dr. Gross there was no evidence at all that such small tumor-particles were not suspended in the juice and did not effect the transplantation of the new formations.

In reference to Dr. Tyson's remarks that the similarity between inflammatory products and tumors was limited to only a few instances, Dr. Formad maintained that this similarity was applicable to the majority of tumors, and, contrary to Dr. Tyson's view, was easily demonstrable,—*e.g.*, in carcinoma. Dr. Formad dwelt upon the gradual transition of inflamed skin into a cancroid, and of a catarrhal inflammation of the stomach or gall-bladder into cancerous growth,—the microscopic picture showing the direct merging of the primary inflammatory changes into cancer, and that it is impossible to point out where the one ends and the other commences.

Dr. Formad could not agree with Dr. Henry that there was necessary "a fibromatous, a lipomatous, an enchondromatous, and other unheard-of forms of inflammation" in accepting the view of an inflammatory origin of tumors. Dr. Formad thought that the ordinary process of interstitial and parenchymatous inflammation and the laws which govern the new formation of tissues are sufficient to explain the histogenesis of the various tumors. Fibroma, he thought, should be regarded as one of the products of a chronic interstitial inflammation; lipoma is nothing else than a uniform fatty infiltration of a fibroma, and a myxoma a mucoid degeneration of the latter. Before we can have adipose tissue we must have connective tissue; and probably all pathological mucous tissue has its origin in a mucoid degeneration of simple connective tisue. The direct transformation of fibrillar connective tissue into cartilage has been proven by several reliable observers. Thus the chondroma is formed. A parallel to this we have in the process of ossification and in the formation of osteoma, etc. Dr. Formad stated that he was acquainted with no real facts that could be brought forward against the view of an inflammatory origin of tumors.

Dr. Formad agreed with Dr. Nancrede

that the quantity of the blood-supply conditioned the growth or the destruction of tissues, and determined frequently the variety of tumor-formation. He maintained, however, that irregularity in the blood-supply had nothing to do with the *causation* of tumors, and that only the inflammatory process was able to prepare a tissue anatomically or to predispose it to tumor-development. The destruction of the endothelial boundaries, the main causative factor, cannot be brought about by irregularity of blood-supply. Continuous hyperæmia, Dr. Formad thought, may bring on—for instance in the mammary gland—a homotopic adenoma, which is only a simple perverted epithelial hypertrophy, and not a true tumor. An injury to the elements of the skin, in the same mammary gland, will, under circumstances referred to, produce a surface epithelioma. An injury affecting the connective tissue of the gland will predispose to sarcoma (rapid effect) or to fibroma (slow effect), while the same cause operating upon the glandular elements proper (destroying the glandilemma) may induce a hard or a soft cancer.

In reference to Dr. Shakespeare's remarks, Dr. Formad stated that he did not mean to declare tumors to be a "natural" termination of inflammation, and that he was perfectly willing to call them a perverted termination of the inflammatory process, occurring only if the healing process is imperfect or retarded.

Tubercle and gumma Dr. Formad did not exclude from the category of tumors, and in them he thought that he had one of the best supports for an inflammatory origin of tumors. Dr. Formad did not think that the causes of the inflammation were here pertinent. In the case of tumor-formation it made no difference whether the operating cause of the inflammation was a specific poison, or a trauma, or anything else. The specific virus is not the cause of the gumma or tubercle, but is the cause of an inflammatory process, which in turn gives rise to the new formation. If the inflammatory changes are arrested, no tumors develop. The excellent series of cases of brain tumors referred to by Dr. Mills, Dr. Formad thought, supported admirably the view propounded.

Dr. Formad expressed his gratitude for the interest taken in the paper by the President and by the members of the Society, and for the many suggestive points ventilated by the discussion.